

Review article

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Surface-enhanced FAST CARS: en route to quantum nano-biophotonics

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Abstract: Quantum nano-biophotonics as the science of nanoscale light-matter interactions in biological systems requires developing new spectroscopic tools for addressing the challenges of detecting and disentangling weak congested optical signals. Nanoscale bio-imaging addresses the challenge of the detection of weak resonant signals from a few target biomolecules in the presence of the non-resonant background from many undesired molecules. In addition, the imaging must be performed rapidly to capture the dynamics of biological processes in living cells and tissues. Label-free non-invasive spectroscopic techniques are required to minimize the external perturbation effects on biological systems. Various approaches were developed to satisfy these requirements by increasing the selectivity and sensitivity of biomolecular detection. Coherent anti-Stokes Raman scattering (CARS) and surface-enhanced Raman scattering (SERS) spectroscopies provide many orders of magnitude enhancement of chemically specific Raman signals. Femtosecond adaptive spectroscopic techniques for CARS (FAST CARS) were developed to suppress the nonresonant background and optimize the efficiency of the coherent optical signals. This perspective focuses on the application of these techniques to nanoscale bio-imaging, discussing their advantages and limitations as well as the promising opportunities and challenges of the combined coherence and surface enhancements in surface-enhanced coherent anti-Stokes Raman scattering (SECARS) and tip-enhanced coherent anti-Stokes Raman scattering (TECARS) and the corresponding surface-enhanced FAST CARS techniques. Laser pulse shaping of near-field excitations plays an important role in achieving these goals and increasing the signal enhancement.

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1 Introduction

At the interface between quantum optics and biophysics lies the emerging exciting field of quantum biophotonics [1]. With new light sources and quantum effects, it is becoming increasingly possible to apply the techniques of quantum spectroscopy to biosciences. A new paradigm shift has been emerging in which the biologists define the parameters that are needed for effective use, and the quantum physicists/engineers design and develop the technology to meet those needs. For example, recent exciting developments of new radiation sources improved the detection of trace impurities via quantum coherence, and related effects improved microscopic resolution (Nobel Prize, 2014). Quantum limits of the existing classical techniques, such as the quantum plasmonic effects in surface-enhanced sensing, have been identified. New technological breakthroughs are needed to address the remaining challenges of nanoscale label-free rapid bio-imaging, with the ultimate goal of obtaining ultrafast molecular movies in living organisms. This requires developing new techniques and pushing the envelope in quantum physics on the one hand and bioscience on the other. In this review, we describe recent progress in surface-enhanced coherent Raman spectroscopy and give a perspective on the use of near-field laser pulse shaping to optimize this technique.

2 Femtosecond adaptive spectroscopic techniques for coherent anti-Stokes Raman scattering (FAST CARS)

Chemically specific optical imaging and sensing techniques play a pivotal role in developing preventive measures to maintain chemical and biological safety and in

biomedical imaging. The detection of a chemically specific target in a harsh and complex environment presents several problems. First, a small number of targeted molecules are not directly accessible for interrogation and yield weak optical signals. On passing through the scattering biological medium, both the incident light and the optical signal are substantially diminished, weakening the signal and diffusing the spatial information about the signal's origin. Second, the chemical specificity has to be maintained in the presence of a substantial background from the surrounding chemicals.

Laser spectroscopy has been widely used for the chemical analysis of living systems. For example, Raman and infrared (IR) spectroscopies can probe the vibrational states of molecules in order to determine, for example, the chemical assay and temperature profile. IR spectroscopy is widely used because it is simple and inexpensive. The major drawback is the high absorption of water in IR. Raman spectroscopy is more complicated but has many advantages and is a more versatile and powerful tool. The major drawback of spontaneous Raman spectroscopy is the weak signal strength. Coherent and stimulated Raman techniques can be used to increase the speed and strength of the imaging signal acquisition by orders of magnitude [2–6]. For example, in the CARS spectroscopy, the signal is proportional to the number of molecules squared as opposed to the linear dependence in the spontaneous Raman technique [7]. However, the nonresonant background also makes a significant contribution.

We have developed a new FAST CARS based on optimal laser pulse shaping for background suppression and demonstrated the first application to the precision sensing of minor molecular species within a highly scattering environment [8], and we also provided a very efficient solution to the problem of detecting and identifying anthrax-type bacterial endospores in real time [9, 10]. Figure 1 shows the basic idea behind the FAST CARS approach. In the case of conventional CARS (Figure 1A and C), two lasers with frequencies ω_p and ω_s (referred to as lasers 1 and 2, respectively) are incident on a sample. When the difference frequency is resonant with some molecular vibration at Ω_R , the sample may also absorb a third photon (either a third laser with frequency ω_{pr} or a second photon from laser 1, $\omega_p = \omega_{pr}$) and generate light at frequency $\omega_{sig} = \omega_p - \omega_s + \omega_{pr}$.

The problem is that the process is masked by the nonresonant four-wave mixing (FWM) background that produces broadband nonlinear generation that can be much larger than the vibrationally resonant CARS signal. FAST CARS was developed for suppressing the nonresonant background based on laser pulse shaping and is shown

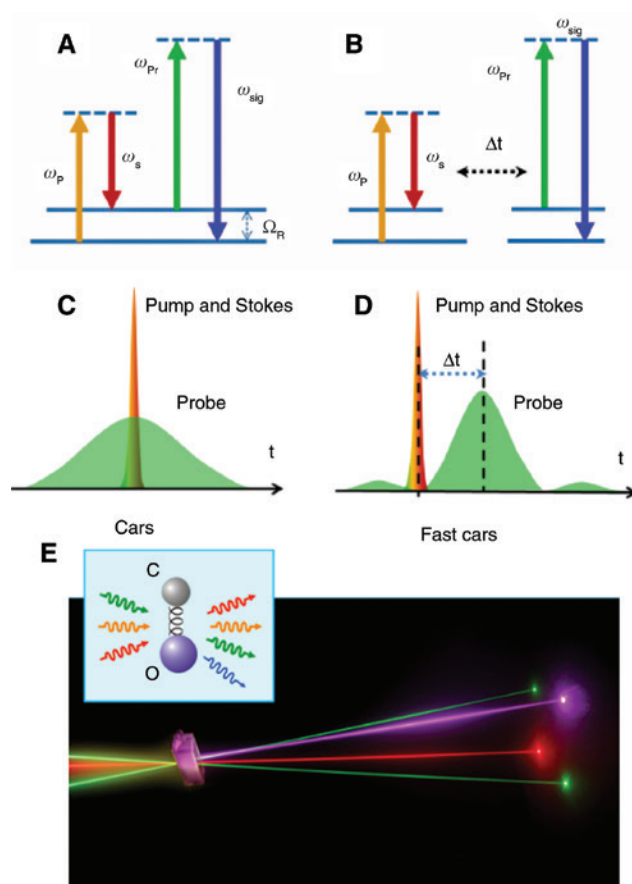


Figure 1: Comparison between the energy level diagrams and the laser configurations for the conventional CARS (A and C) and the time-resolved FAST CARS (B and D) spectroscopies. (E) Sketch of the laser beam configurations shows the pump (green), Stokes (red) and probe (green) laser beam incident on a sample generating the FAST CARS beam (blue). The inset shows a vibrating molecule emitting coherent signals. Adapted from Voronine et al. [1] and Shen et al. [11].

in Figure 1B and D [8, 9]. Here, the laser pulses 1 and 2 are applied to the sample first, and the optimally shaped laser pulse 3 is delayed. When laser 3 is applied to the sample and lasers 1 and 2 are not, the nonresonant processes do not occur. However, lasers 1 and 2 will have excited coherence between the vibrational levels in the molecule for which they are Raman resonant. If this coherence lasts longer than the delay, laser 3 will scatter from the coherence and still produce the FAST CARS signal at ω_{sig} . Spectral and temporal laser pulse shapes may be optimized to minimize the nonresonant background, for example, by placing lasers 1 and 2 (pump and Stokes) in the temporal node of the sinc-shaped pulse 3 (probe), and to enhance the resonant vibrational signal (Figure 1D).

Spontaneous Raman microscopy has been widely applied for the imaging of a variety of materials including

biological systems [12–15]. This has been a challenge due to the small Raman cross sections of biomolecules, leading to weak signals and long image acquisition time, in some cases taking multiple hours. Coherent Raman imaging provides a significant increase in imaging speed [6]. However, as the coherent Raman signal is proportional to $N(N-1)$, where N is the number of molecules [7], the coherence enhancement decreases with the decrease of N and vanishes with $N=1$, that is, for the case of a single molecule. This makes it challenging to perform coherent Raman imaging at the nanoscale when the number of molecules N is small. Other Raman signal enhancement techniques, such as the plasmonic surface enhancement, may be combined with FAST CARS to further improve the sensitivity of nanoscale bio-imaging.

3 Quantum limits of surface enhancement

Nanoscale confinement of optical fields using plasmonic nanostructures provides an effective strategy for enhancing spectroscopic detection and imaging [16]. Localized surface plasmon resonances (SPRs) of metallic nanostructures and propagating surface plasmon polaritons (SPPs) may be used to obtain surface-enhanced Raman scattering (SERS) signals [17–19]. The SERS effect is based on two mechanisms: electromagnetic mechanism (EM) and chemical mechanism (CM). The former is due to the local enhancement of the EM fields in the vicinity of the plasmonic nanostructures. The latter is due to the chemical interactions between the sample and the substrate, leading to the modification of the sample polarizability and the enhancement of the Raman scattering cross section. EM enhancement is usually the dominating effect in gold and silver nanostructures, leading to many orders of magnitude signal enhancement and sensitivity, which approaches the single-molecule limit [20–25].

There was much previous work on the applications of SERS to biosensing. However, less work was performed on the surface-enhanced nanoscale bio-imaging. There are several successful examples of proof-of-principle demonstrations of nanoscale bio-imaging using tip-enhanced Raman scattering (TERS) [26–33]. TERS is a combination of SERS and scanning probe microscopy, such as atomic force microscopy (AFM) and scanning tunneling microscopy (STM) [34–37]. AFM and STM performed with plasmonic probes made of gold and silver illuminated by laser radiation provide simultaneous topographic and

spectroscopic information with nanometer-scale spatial resolution. The Raman signal enhancement is based on the SERS EM and CM. The spatial resolution depends on the size of the probing tip apex, which may range from tens of nanometers down to a few atoms. A single hot spot generated at the tip apex provides both the Raman signal enhancement and the high spatial resolution. Large signal enhancement is crucial for achieving high imaging contrast and is strongly dependent on the tip design. Recent experiments demonstrated an extraordinarily high spatial resolution down to the sub-nanometer scale on carbon nanotubes (CNTs) [38] and porphyrin molecules in ultrahigh vacuum [39] and on DNA under ambient conditions [40]. TERS imaging was demonstrated on a variety of systems, but it is still a challenge for routine clinical bio-imaging. TERS imaging of a living biological cell has not yet been demonstrated. Such an experiment would require high-quality tips with strong signal enhancement for rapid non-destructive imaging and possible additional signal enhancement using other mechanisms such as resonance and/or coherence enhancements. The combination of the surface and the coherence enhancements is the focus of this review.

To better understand and make use of the SERS effect, we consider the limits of the surface enhancement, both EM and CM. Single plasmonic nanostructures such as silver and gold nanoparticles (NPs) can enhance the electromagnetic fields. However, the largest enhancement may be obtained by the coupling of multiple NPs [41–43]. Resonant optical dipole nanoantennas show strong near-field enhancement in the nanometer-size gap between NPs [44–48]. A similar behavior may be observed in TERS when the plasmonic tip is coupled to a metallic [49–52] or semiconductor [53] substrate. Figure 2A shows the schematics of the classical and quantum gap-mode TERS configurations. In the classical case, the gold tip induces an image dipole in the gold substrate, leading to the strong electric field enhancement and the corresponding Raman signal enhancement, which increases for the decreasing tip-sample distance. Classically, smaller gaps correspond to larger field enhancement. However, for the gaps smaller than ~ 1 nm, quantum tunneling (QT) of the electrons through the gap between the tip and the substrate leads to the decrease of the surface electron density of the tip and the corresponding decrease in the electric fields (Figure 2A, quantum regime). The quantum plasmonic effects were predicted [55–57] and experimentally demonstrated in systems of metallic NPs [58–62] and in TERS experiments using metallic tips and substrates [54, 63]. Figure 2B shows the tip-sample distance dependence of the gold photoluminescence signal

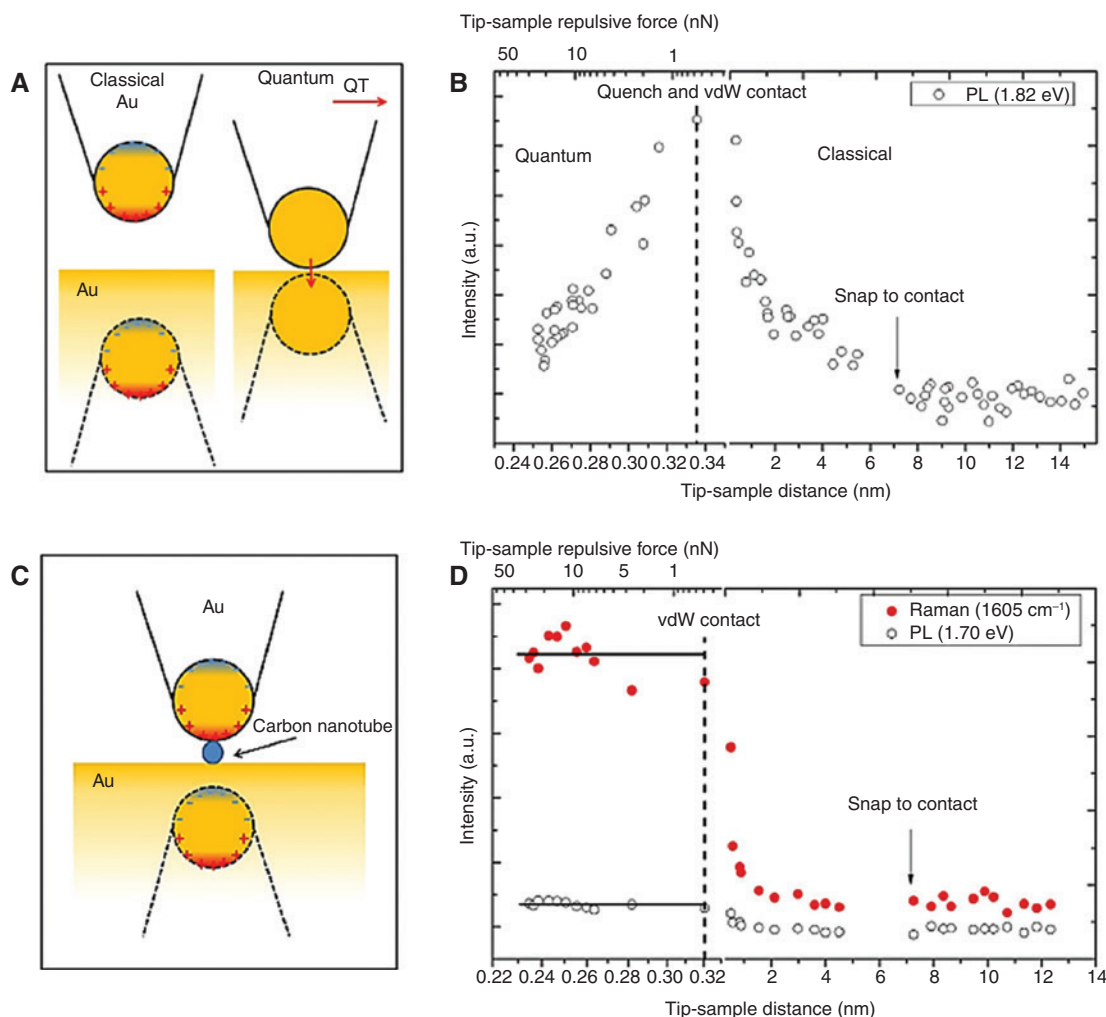


Figure 2: Quantum limits of surface enhancement revealed in (A) tip-enhanced photoluminescence (PL) of gold and (C) TERS signals of CNTs. Tip-sample distance dependence of the optical signals from the gold tip near the atomically flat gold substrate without (B) and with the CNT (D) junctions. PL and Raman signals are shown as open and red filled circles, respectively. Vertical dashed lines denoted by “Quench” and “vdW Contact” show the moments at which the signals begin to decrease and the tip-sample distance approaches the vdW diameter, respectively. Classical and quantum coupling schemes of the gold tip (A) and CNT (C) on gold substrates. Red arrow represents the QT current. Dashed lines show tip images in the substrates. Adapted from Zhang et al. [54].

before (classical regime) and after (quantum regime) the van der Waals (vdW) contact distance of ~ 0.33 nm. These two regimes correspond to the increase and decrease of the field enhancement with the decrease of the tip-sample distance, respectively. Figure 2C and D shows the schematic and tip-sample distance-dependent optical signals for the gap-mode TERS of a CNT, respectively. No significant quantum plasmonic quenching is observed after the vdW contact due to the larger Schottky barrier of the CNT which prevents electron tunneling. The unprecedented distance dependence control with sub-Angstrom resolution was obtained in these picometer-scale indentation experiments (Figure 2B and D). They give insights into the limits of the surface enhancement and may guide the

optimization of the nanoscale bio-imaging experiments. These results were made possible due to the recent progress in the scanning probe microscopy instrumentation with improved stability and distance dependence control of the combined state-of-the-art commercial systems (AIST-NT and Horiba).

Chemical enhancement effects have been observed in metallic systems but are usually weaker compared to the EM enhancement and are often masked. Recently, dramatic Raman signal enhancement was reported on ordered two-dimensional (2D) layered materials (graphene, MoS_2 and h-BN) [64–66]. The observations showed great promise to take advantage of the Raman scattering to identify chemical species using non-metallic

substrates. The enhancement on 2D layered semiconductor materials is dominated by the CM based on the change of the molecular polarizability caused by chemical interactions between the adsorbed molecules and the substrate. Various explanations of the CM were proposed, including (1) charge transfer resonances involving the transfer of electrons between the molecule and the conduction band of the substrate, and (2) molecular resonances [67–73]. Two-dimensional layered semiconductor materials provide excellent templates for studying the CM. CM enhancement may be increased by optimizing the electronic structure of the semiconducting substrates. These phenomena open the door to dramatically enhance Raman signals using both CM and EM effects.

Even when the quantum limit of the surface enhancement is reached, the optical signals may be further enhanced by using other mechanisms such as quantum coherence. Next, we consider the best-of-both-worlds combinations of the surface and coherence enhancements using surface-enhanced coherent Raman spectroscopy.

4 Toward best-of-both-worlds surface-enhanced coherent Raman scattering

Quantum nano-biophotonics addresses the challenges of time-resolved nanoscale bio-imaging by taking advantage of various signal enhancement techniques such as CARS and SERS discussed above. In addition, high temporal resolution may be achieved using ultrashort laser pulses. The laser pulse shape may be optimized to suppress the nonresonant background and to control selectivity via the enhancement of the molecular signals. Various coherent nonlinear Raman techniques may be combined with surface enhancement to achieve an astonishing sensitivity [74]. For example, surface-enhanced femtosecond stimulated Raman scattering spectroscopy was developed using gold nanoantennas with embedded reporter molecules [75]. Various versions of surface- and tip-enhanced coherent anti-Stokes Raman scattering (SECARS and TECARS) techniques were demonstrated on ensembles down to a few and even single-molecule sensitivity. Several recent review papers described these developments [44, 74, 76–80]. Here, we focus on the SECARS techniques in which the physics of the interplay between the coherence and the surface enhancement is, in our opinion, most clear.

4.1 SECARS

The first experimental demonstrations [81, 82] and theoretical analysis [83] of SECARS were followed by several attempts to simulate [84, 85] and improve the signal enhancement [86–89], optimize substrates [85, 90–93], add temporal resolution [94, 95], suppress the nonresonant background [85, 94, 96], achieve single-molecule sensitivity [95, 97, 98] and perform microscopic [99, 100] and nanoscale bio-imaging [101–104]. These studies revealed and addressed the controversies such as the lower experimental enhancement factors (EFs) than those expected in theory, the comparison between SERS and SECARS, the limited reproducibility, the challenges of single-molecule detection and biological applications. The latter have been one of the main motivations for the development of SECARS. Here, we review these challenges and speculate on future perspective solutions.

Large surface EFs are expected in SERS and SECARS. The EM enhancement via SPR field enhancement and CM enhancement via charge transfer both contribute to the EFs as discussed above, with the larger effect of the EM on noble metal substrates. The EFs for SERS are defined with respect to the spontaneous Raman scattering (SpRS). However, the SECARS EFs can be defined with respect to (i) conventional CARS without the surface enhancement by plasmonic nanostructures ($EF_{\text{SECARS/CARS}}$), or with respect to (ii) SERS without the coherence enhancement ($EF_{\text{SECARS/SERS}}$) or with respect to (iii) SpRS without both surface and coherence enhancements ($EF_{\text{SECARS/SpRS}}$). The latter is the total SECARS EF, which has all the contributions of the various enhancement mechanisms. These EFs are summarized in Table 1, where the column labels indicate the techniques whose EFs are considered with respect to the corresponding techniques with the row labels. The theoretically expected EF values are shown in bold, and the corresponding experimentally obtained EF values are given in parentheses together with the plasmonic substrates, type of SECARS and references. Femtosecond SECARS is based on the femtosecond laser pulses, while the FAST SECARS is based on the combination of femtosecond and shaped picosecond laser pulses. These techniques and experimental demonstrations are discussed in more detail below.

The coherence enhancement of CARS with respect to the SpRS may reach $\sim 10^6$ and depends on the squared number of molecules [7]. The surface enhancement may reach many orders of magnitude due to the nonlinear dependence of SECARS on the local electric fields (Figure 3) [91]. The EM enhancement leads to EFs which

Table 1: EFs of various spectroscopic techniques with the surface and/or coherence enhancement (column labels) with respect to the techniques without these enhancements (row labels) based on the theoretical expectations (bold) and experimentally observed (in parentheses).

	CARS	SERS	SECARS
SpRS	10^6 (10^6 , various samples [7])	10^4–10^{12} (10^{10} , various samples [105])	10^{14}–10^{30} (10^{11} , plasmonic quadrumer, fsec SECARS [98])
CARS	–	–	10^8–10^{24} (10 , colloidal NPs, fsec SECARS [87]; 10^5 , deterministic, fsec SECARS [91]; 10^7 , random aggregated NPs, FAST SECARS [94])
SERS	–	–	10^{10}–10^{18} (10^3 , deterministic, fsec SECARS [91])

fsec, Femtosecond.

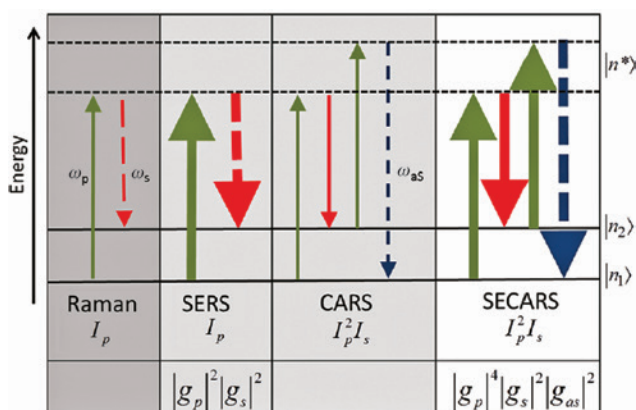


Figure 3: Surface and coherence enhancement of Raman signals. Schematic band energy diagram showing transitions in different Raman processes and their dependence on the pump (I_p) and Stokes (I_s) intensities and the corresponding local electric field enhancement (g). Adapted from Steuwe et al. [91].

are proportional to the near-field EFs (g) in hot spots of plasmonic nanostructures, which can reach values $g \sim 10^1$ – 10^3 depending on the geometry and composition. The corresponding $\text{EF}_{\text{SERS}} \propto |g_p|^2 |g_s|^2$ can reach values of 10^4 – 10^{12} , where g_p and g_s are the pump and Stokes near-field EFs, respectively. Such large EFs were experimentally observed [105]. However, the SECARS EFs have both surface and coherence contributions of $\text{EF}_{\text{SECARS/CARS}} \propto |g_p|^4 |g_s|^2 |g_{as}|^2$ and $\text{EF}_{\text{SECARS/SERS}}$, which can theoretically reach $\sim 10^8$ – 10^{24} and $\sim 10^{10}$ – 10^{18} , respectively. Here, g_{as} is the anti-Stokes signal near-field EF. Therefore,

the total SECARS EF over spontaneous Raman, denoted $\text{EF}_{\text{SECARS/SpRS}}$, can reach $\sim 10^{14}$ – 10^{30} , which has not yet been experimentally demonstrated. Recent progress in instrumentation and nanofabrication has been pushing these EFs up toward theoretical predictions. Further improvements are expected from a better understanding of the experimental challenges, inhomogeneous sample properties, effects of laser pulse shaping and chemical interactions. Some of these are addressed in more detail below.

As one of the SECARS schemes, surface-enhanced FAST CARS is developed to suppress the unwanted nonresonant background. Therefore, there is a competition of two effects which determines the signal-to-noise ratio of the surface-enhanced FAST CARS signals, namely, the signal enhancement and the nonresonant background suppression. The background suppression may be achieved by the temporal delay of the pump/Stokes and probe laser pulses. However, this often decreases the overall signal due to the temporal decay of the coherence. In practice, an optimal time delay is used to obtain the maximum signal with the minimum background. On the other hand, there are also techniques in which the enhancement may be optimized at the zero time delay with the presence of the nonresonant background. For example, heterodyne CARS techniques used in broadband CARS microscopy [106–110] may be combined with SERS and TERS to improve signal enhancement. In heterodyne CARS, the weak molecular resonant signals may be enhanced by coherently mixing with the nonresonant background. Previously, we succeeded in eliminating the FWM background in surface-enhanced FAST CARS [9, 10, 94]. However, by properly introducing some background and controlling the phase, it may be possible to improve the detection sensitivity. The interference between the coherent resonant signal and the coherent nonresonant background may be controlled by phase and amplitude pulse shaping. For example, this control may be achieved by making fine adjustments to the probe field shape [111]. Spectral asymmetry of the probe may produce a stronger temporal probe field at the node and the correspondingly stronger FWM background which provides flexibility of controlling both the phase and intensity of the heterodyne signals. Near-field pulse shaping needs to be carefully designed to optimize the EFs in surface-enhanced broadband heterodyne CARS.

Another factor which needs to be carefully considered is the saturation of the coherent Raman transitions in analogy to the corresponding saturation of the Raman gain in stimulated Raman scattering [112, 113]. Here, because of the strong field enhancement, the Raman signal may get saturated before reaching the predicted

30 orders of magnitude enhancement. This effect will be stronger in molecular systems with large Raman scattering cross sections.

4.2 SECARS on colloidal NPs

A single plasmonic sphere is the simplest model system for SECARS. Theoretical analysis estimated the EF value of 10^{12} for a monolayer of benzene on a silver particle [83]. However, the experimental demonstration of this configuration is not trivial. A simpler experimental approach is an ensemble of the colloidal plasmonic spheres dispersed in a neat liquid of interest. It was also considered in the first theoretical SECARS analysis and compared with the single sphere model [83]. Lower experimentally observable EFs were predicted based on the averaging over the ensemble of spheres and competition with the background bulk CARS signal. The NP concentration dependence was used to estimate the minimal concentration needed to detect the SECARS signal and was found to be $\sim 10^{-5}$ g/cm³. The sphere ensemble approach is particularly significant for the investigation of biological systems with preferable minimized sample perturbation. However, the challenges mentioned need to be carefully considered in the design of biological applications. Another challenge is the potential sample degradation due to the high power of ultrashort laser pulses. One important difference between the typical SERS and SECARS experiments is that the former is usually performed using continuous wave lasers, while the latter is performed using ultrashort laser pulses. Therefore, special attention has to be paid to the heat generation in the SECARS experiments and the heat resistance of the investigated sample system. Two pioneering experimental works investigated SECARS on colloidal solutions using nanosecond [82] and femtosecond laser pulses [87].

Nanosecond SECARS experiments on benzene, chlorobenzene and toluene were performed in colloidal solutions of silver NPs and revealed up to $\sim 10^2$ EFs and an improvement in signal-to-noise ratio [82]. The SECARS signals were collected at right angles with respect to the pump and Stokes beams, which were incident on a sample at a small angle (1° – 3°). The pump wavelength dependence showed the maximum signal enhancement at ~ 500 nm, which was red shifted with respect to the SPR of the silver colloid. This first demonstration of the SECARS in a colloid solution did not perform a careful sample characterization or make a quantitative comparison with the previous theoretical predictions. The authors noted a narrower pump excitation wavelength profile than what was expected from the width of the SPR. They explained

it by the more restricting resonance conditions of the four photons involved in the CARS process. For example, the red-shifted detuning of the pump wavelength away from the SPR requires even further detuning of the Stokes wavelength, which leads to a fast decrease of the SECARS signal. This indicated the need for improving the design of plasmonic nanostructures to optimize the SPR frequency and width.

Femtosecond SECARS experiments in silver colloids were performed on pyridine and showed only a factor of 10 EFs for the pump wavelength of 550 nm for the SECARS collected in the forward direction and no enhancement for other pump wavelengths [87]. Another difference from the nanosecond SECARS was the absence of the signal enhancement collected at right angles. Interestingly, the observed SERS EFs of $\sim 10^4$ from the same silver colloid were three orders of magnitude larger than the corresponding SECARS EFs. The comparison of the SERS and spontaneous Raman spectra of pyridine in the silver colloid is shown in Figure 4A. In contrast, smaller enhancement is shown for the SECARS signals with different concentrations of silver colloid in Figure 4B. Note that the spectra in Figure 4A and B have mismatched x axes. The two strongest vibrational transitions of pyridine around 1000 cm⁻¹ are clearly seen in the SERS spectra but are less resolved in the SECARS spectra due to the lower spectral resolution from the broadband femtosecond laser pulses. Also, the surface-enhanced nonresonant FWM background may contribute to the observed SECARS spectra [114–117]. The concentration dependence showed the maximum SECARS enhancement for 10% concentration of the silver colloid. The enhancement decreased for the larger concentration, probably due to the scattering of the lasers and signal away from the phased-matched forward direction by the silver NPs. These experiments indicated the dependence of the SECARS signals on several parameters such as the properties of the silver colloids, concentration, laser wavelength, intensity and phase matching. Optimization of these conditions is challenging and might be more easily achieved in other SECARS configurations such as in random aggregates of NPs or in deterministically designed nanostructures. These are discussed next.

4.3 SECARS on random nanostructures with local phase variations

The problem of small EFs in femtosecond SECARS on colloids was addressed by optimizing the random gold NP self-assembly deposited on glass substrates [90]. SECARS of oxazine 720 was measured as a function of the number

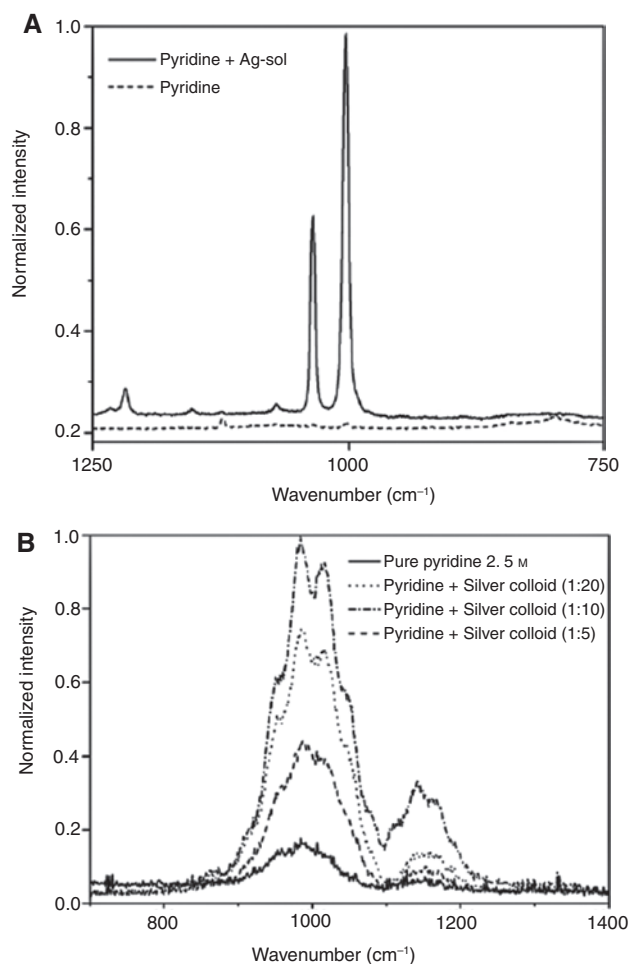


Figure 4: SECARS on colloidal NPs.

(A) Raman spectra of pyridine recorded without (dashed, spontaneous Raman) and with (solid, SERS) the addition of silver colloid. (B) Femtosecond SECARS spectra of pyridine for different concentrations of silver colloids (dashed curves) compared with the conventional CARS spectrum of pyridine alone (solid curve). Note that the spectra in (A) and (B) have mismatched x axes. Adapted from Namboodiri et al. [87].

of gold NP depositions, and the maximum $EF_{\text{SECARS/CARS}}$ of 10 was obtained for 11 depositions from the 1600 cm^{-1} signal. One of the reasons for such small EFs can be the spatial averaging over a large surface area, which includes locations with and without so-called “hot spots,” that is, locations with large EFs due to small inter-particle gaps and SPR matching the incident laser wavelength and CARS signals. The EF was optimized by increasing the number of NP depositions, leading to a larger number of hot spots and to the optimal match of the SPR. However, small EFs and large spatial variations from area to area were observed even in the optimized substrates. Other possible reasons could be the nonresonant background contributions and local phase variations as discussed next.

Many parameters play a role and may be optimized in femtosecond SECARS experiments. Nano-optical bio-sensing and imaging require large signal enhancement, small background, short detection time and high spatial and spectral resolution. Ultrashort laser pulses provide unique opportunities to detect nonlinear optical signals and to study ultrafast time-resolved dynamics. They also provide a range of control parameters such as the wavelengths, polarizations, spectral and temporal amplitudes and phases to optimize the nonlinear signals. Recently, we developed a surface-enhanced FAST CARS technique which is a type of the time-resolved SECARS (tr-SECARS) where the pump and Stokes pulses are temporally delayed with respect to the shaped probe pulse (Figure 5A) [94]. The probe pulse was shaped as a sinc function using a home-built pulse shaper in order to place the pump and Stokes pulses in the temporal node of the probe to suppress their temporal overlap and the nonresonant FWM background. A similar FAST CARS setup was previously used to detect Raman signals from bacterial endospores [9, 10]. Our surface-enhanced FAST CARS technique (also abbreviated as FAST SECARS) increased the conventional

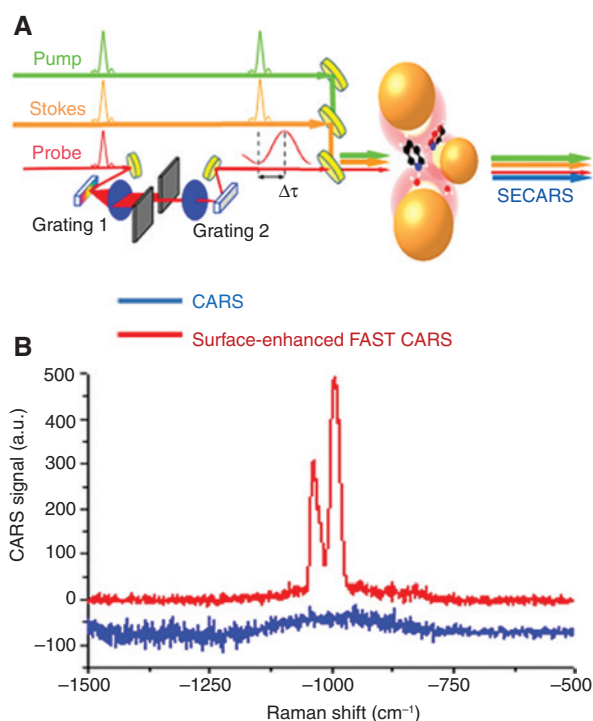


Figure 5: Surface-enhanced FAST CARS on random nanostructures. (A) Experimental scheme of the surface-enhanced FAST CARS spectroscopy. (B) Surface-enhanced FAST CARS (red) reveals traces of hydrated pyridine molecules on the surface of gold NP aggregates with higher sensitivity than the conventional CARS (blue). Adapted from Voronine et al. [94].

CARS signal intensity by $EF_{\text{SECARS/CARS}}$ of $\sim 10^7$ and was used to detect trace amounts of water on the surface of random aggregated gold NPs (Figure 5B). A spectral resolution of $\sim 3 \text{ cm}^{-1}$ was achieved by narrowing the bandwidth of the probe pulse using the slit of the pulse shaper. This facilitated the observation of the 7 cm^{-1} spectral shift of the position of the pyridine ring breathing mode due to the interaction with water. The FAST SECARS temporal signal provided direct observations of the dephasing dynamics of the pure bulk pyridine and the surface-bound water-pyridine complexes. The latter exhibited shorter dephasing times compared to the bulk pyridine. This time-resolved configuration of the SECARS provides a possibility to study biological systems simultaneously with a high

spatial and temporal resolution. The aggregated colloidal gold NPs showed large SECARS EFs which, however, still represented average quantities over micrometer-scale observation areas and were smaller than expected. We performed additional investigations by analyzing the spatial dependence of the SECARS EFs and local phases.

We also measured the spatial variation of the shape of the FAST SECARS spectra of pyridazine on randomly aggregated gold NPs and obtained insights into the nature of low SECARS EFs [85]. Figure 6A shows a schematic SECARS process where three ultrashort laser beams (pump, Stokes and probe) excite the sample of aggregated gold NPs on a glass substrate and generate locations of enhanced local fields (hot spots) with different phases

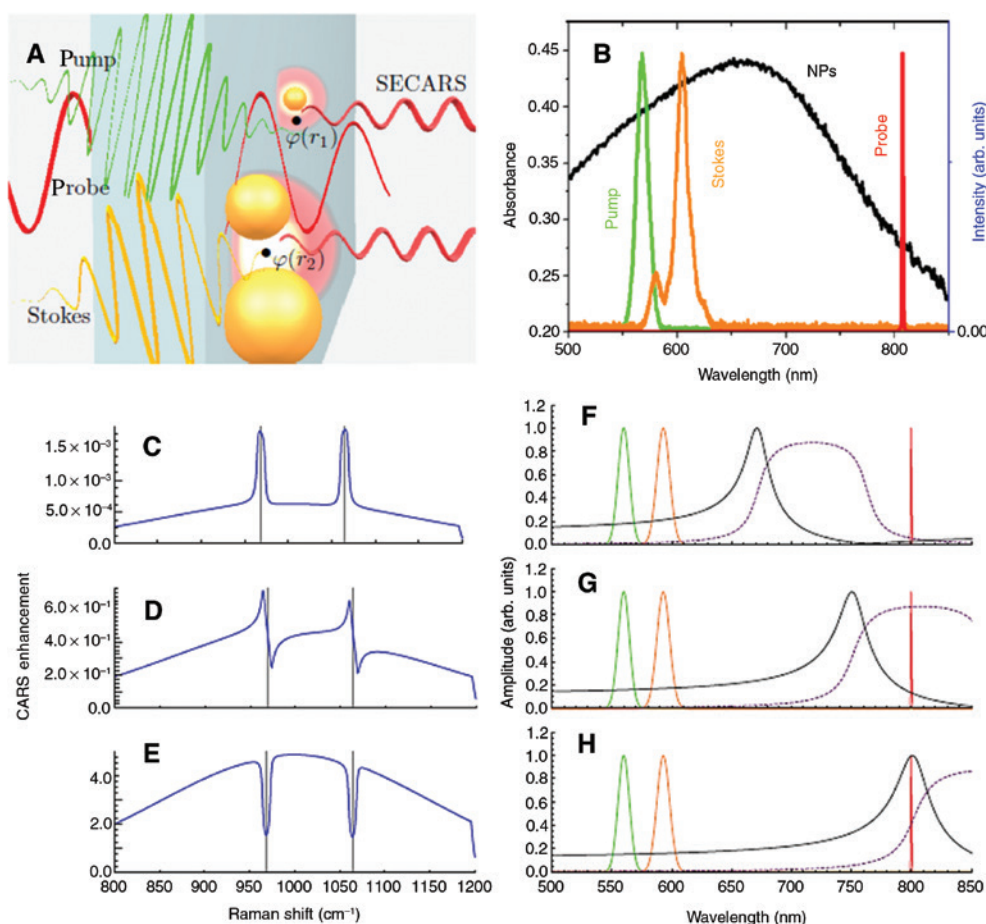


Figure 6: Nature of SECARS.

(A) Schematic picture of the SECARS process: three ultrashort laser pulses (pump, Stokes and probe) are focused on the sample of randomly aggregated gold NPs on the surface of glass inducing SECARS signals from pyridazine molecules in different spatial locations with different local phases $\phi(r)$ which lead to different spectral shapes and low average EFs. (B) Average absorbance spectrum of the aggregated gold NPs (black, NPs) overlapping with the laser pulse spectra used in the SECARS experiments. (C–E) SECARS spectra of pyridazine simulated with SPR wavelengths at 672, 751 and 802 nm, respectively. (F–H) The corresponding electric field amplitudes of the incident pump (green), Stokes (orange) and probe (red) laser pulses with normalized amplitudes (solid black) and phases (purple dashed) of the local field enhancement. For certain ratios of the field amplitudes and certain local phases, it is possible to obtain almost complete destructive interference between the incident and enhanced local fields leading to the formation of “cold spots” with negative EFs. Adapted from Hua et al. [85].

$\varphi(\mathbf{r}_j)$. Averaged SECARS signals obtained from a few-micrometer-size area contain many hot spots with different local phases leading to different SECARS line shapes (e.g. peaks, dips and dispersive line shapes) which may destructively interfere, leading to low average EFs. Figure 6B shows the average absorbance spectrum of the aggregated gold NPs (black, NPs) overlapping with the laser pulse spectra used in the SECARS experiments. The broad absorbance spectrum consists of an average of many SPR spectra with different frequencies and spectral phases which modify the phases of the resulting SECARS signals (Figure 6F–H) and the SECARS spectral line shapes (Figure 6C–E). For certain ratios of the nonresonant background and number of surface pyridazine complexes and for certain SPR positions with respect to the laser beams, it is possible to obtain almost complete destructive interference between the incident and enhanced local fields, leading to the formation of “cold spots” with negative EFs (Figure 6C and F). Better design of the plasmonic nanostructure substrates and better control of the laser excitation are needed to maximize the SECARS EF via constructive interference.

We also observed more complex line shapes in the SECARS of pyridazine on aggregated gold NPs than were expected based on the simulations described above [96]. In addition to the peaks, dips and dispersive line shapes, we observed a peculiar “peak-dip” line shape which consisted of both a peak and a dip at two closely spaced pyridazine transitions. This line shape may be explained as resulting from the interference of signals from two different molecular complexes, one of which is present in bulk and the other is near the plasmonic surface. The peak-dip effect may be present if these complexes have different relative ratios of the intensities of the Raman signals from different transitions. The complex SECARS line shapes are sensitive to the minor differences in the intensity ratios and may be used as sensitive probes of molecular environment. The SECARS EFs may be improved by optimizing the nanostructured substrate design, by the control of local phases by laser pulse shaping and by the optimization of the sample conditions, such as the contributions of solvent, and various molecular complexes. Next, we discuss these approaches.

4.4 SECARS on deterministic nanostructures

The SECARS substrates may be optimized by focusing either on a single plasmonic nanostructure or on a periodic nanostructure array. Previous work on single plasmonic nanostructures showed first SECARS demonstrations of

adenine on isolated gold NPs with $EF_{\text{SECARS/CARS}}$ of $\sim 10^3$ [86], followed by tip-enhanced implementations of SECARS on DNA, CNTs and subcellular organelles using plasmonic tips [80, 88, 101, 103, 104] with $EF_{\text{SECARS/CARS}}$ between ~ 10 and 10^6 , and approached single-molecule sensitivity using plasmonic NP dimers [89, 95] and quadrumers [98] with $EF_{\text{SECARS/SPRS}}$ of $\sim 10^{11}$, approaching the theoretical limits.

The second approach to optimize the SECARS substrates is via the design of periodic arrays of plasmonic nanostructures. Cross-dipole nanoantennas were previously arranged in a 2D array pattern providing the optical near-field enhancement of ~ 128 in the hot spots at the centers of the cross-antennas (Figure 7) [92]. We theoretically estimated $EF_{\text{SECARS/CARS}}$ between $\sim 10^{11}$ and 10^{12} for typical values of SPR line widths [85]. Similar substrates made of crisscross dimer arrays were theoretically investigated and showed large field enhancements and same spatial hot spot regions for the three incident fields with $EF_{\text{SECARS/CARS}}$ of $\sim 10^{16}$ [118]. The cross nanoantennas provide opportunities to engineer the near-field polarization profile [119] and to optimize the cross-polarized SECARS signals. Nanoantenna array metasurfaces [120] may be

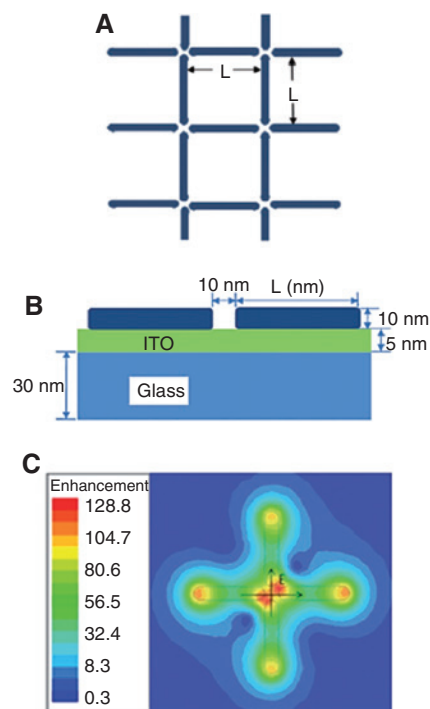


Figure 7: Plasmonic metasurface for SECARS.

(A) Cross-dipole metasurface with dipole arms arranged in an array pattern. (B) The array elements are gold strips on an indium tin oxide (ITO)/glass layer illuminated from the top by a 1000-nm plane wave. (C) Near-field enhancement map in a plane 15 nm above the ITO surface shows two orders of magnitude enhancement of the electric field in the dipole gap. Adapted from Nevels et al. [92].

designed to optimize the amplitude and phase properties of the SECARS substrates.

The first experimental demonstration of the SECARS on periodic plasmonic substrates was performed on fabricated nanovoid surfaces and commercial (Klarite) substrates with $EF_{\text{SECARS/CARS}}$ of $\sim 10^5$ and $EF_{\text{SECARS/SERS}}$ of $\sim 10^3$ (Figure 8) [91]. Femtosecond laser pulses were focused to $\sim 1\text{-}\mu\text{m}$ spots on the nanovoid surfaces with variable nanovoid thickness and diameters between 400 and 1000 nm, and on the Klarite surface consisting of micrometer-size pyramidal pits. The substrate structural parameters were varied to optimize the SECARS signals by matching the SPR frequencies to the incident lasers. The plasmon-aided mechanism was proposed (Figure 8A), in which the incident photons are coupled to plasmons which generate coherent anti-Stokes-shifted plasmons that are coupled into the outgoing SECARS photons. Despite the low spectral resolution of $\sim 50\text{ cm}^{-1}$ due to the broadband excitation and contributions of the surface-enhanced FWM background, the authors were able to prove the molecular selectivity by distinguishing the SECARS spectra of several molecules (Figure 8B and C). They detected submonolayer concentrations of cyanide and achieved close to single-molecule sensitivity. The advantage of the nanovoid

substrates was their broadband SPR range, which can match the incident laser and signal wavelengths in the same spatial location. The design of such substrates may be further optimized for the purpose of achieving optimal SECARS EFs.

4.5 Surface-enhanced CARS of single and/or few molecules

tr-SECARS microscopy was for the first time demonstrated on *trans*-1,2-bis-(4-pyridil) ethylene (BPE) molecules attached to single gold plasmonic dimers encapsulated in porous silica shells (Figure 9) [95]. The observed SECARS spectra were attributed to the ensembles of a few and even single molecules in the gaps between the plasmonic nanoantenna junctions. The evidence for single-molecule sensitivity was obtained by analyzing the temporal traces of the vibrational beating signals excited on and off resonance with the BPE vibrational transitions using time-delayed pump/Stokes and probe pulses (Figure 9). The observed vibrational quantum beats of the ensemble bulk signals decayed after $\sim 1\text{ ps}$. However, some of the single nanostructure signals persisted for the 10-ps duration of

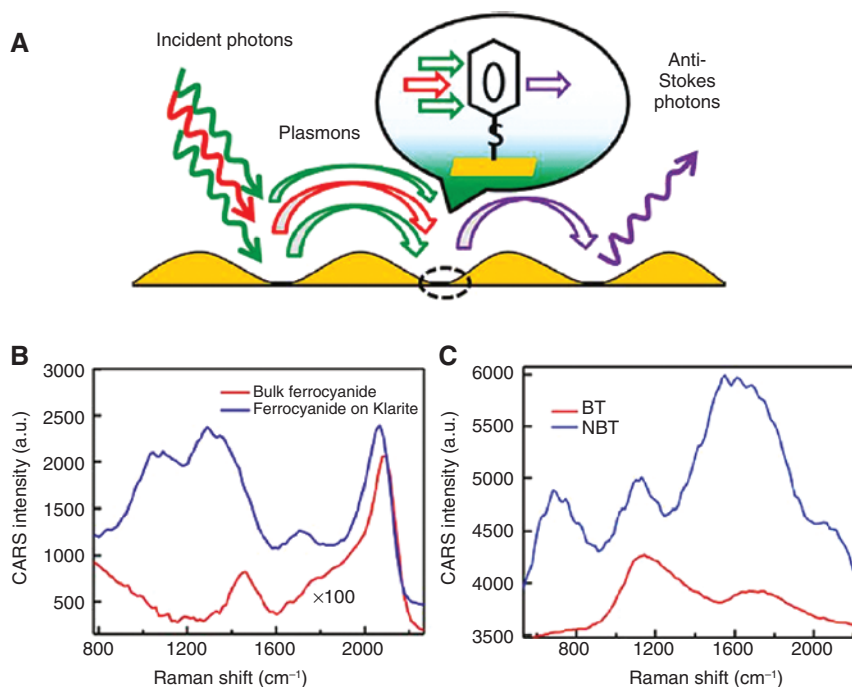


Figure 8: SECARS on a deterministic substrate.

(A) Schematic of plasmon-aided SECARS on a deterministic substrate: incoming pump and Stokes radiation couples into surface plasmons that interact coherently with molecules on the surface and scatter into the outgoing CARS photons. (B) SECARS spectrum (blue) of submonolayer ferrocyanide on a plasmonic substrate (Klarite) compared with the CARS spectrum (red) of the same bulk ferrocyanide. (C) SECARS spectra of nitrilobenzenethiol (NBT) and benzenethiol (BT) on Klarite. Adapted from Steuwe et al. [91].

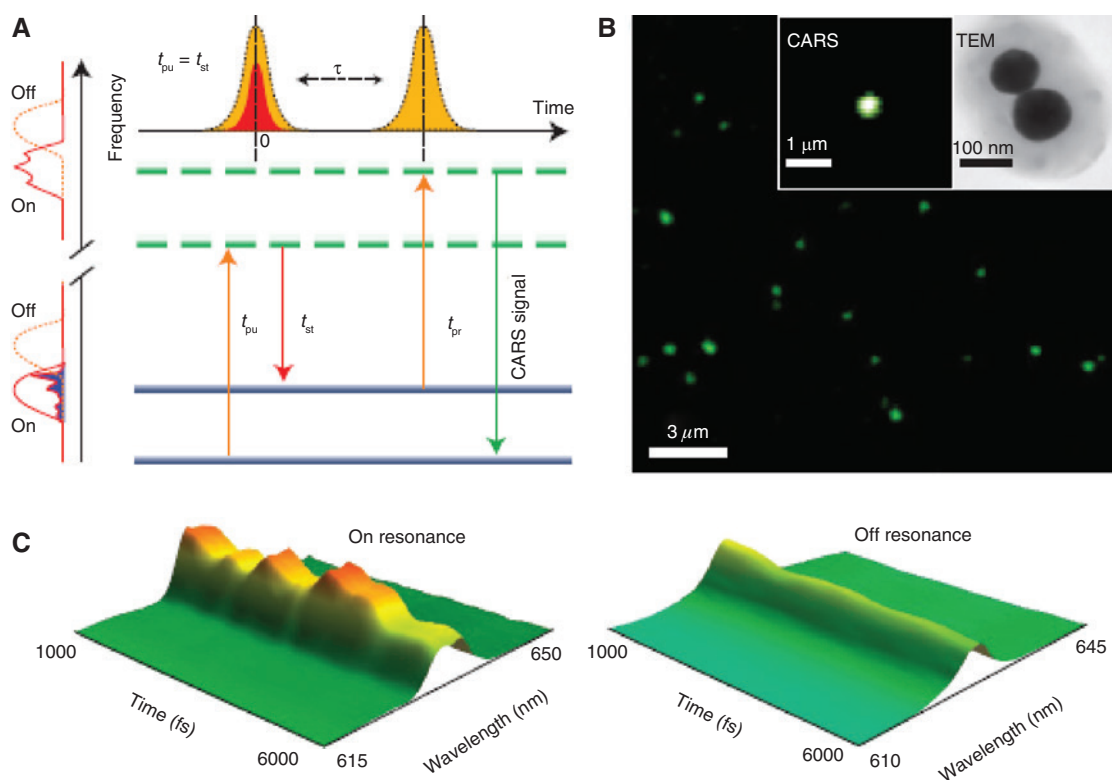


Figure 9: tr-SECARS microscopy of BPE molecules on single plasmonic dimers.

(A) The energy diagram shows the SECARS excitation scheme with the time delay τ between the pump/Stokes pair and the probe pulse.

(B) CARS image of isolated plasmonic dimers. Inset: CARS image of a single dimer and the corresponding transmission electron microscopy image. (C) Spectrally and temporally resolved CARS signals of a single dimer acquired on (left) and off (right) resonance. Quantum beats corresponding to the molecular SECARS signals disappear in the off-resonance signals. Adapted from Yampolsky et al. [95].

the experiment. This was attributed to the absence of the dephasing and, therefore, the single-molecule origin of the SECARS signals.

Another evidence for single-molecule SECARS sensitivity was obtained from para-mercaptoaniline (p-MA) and adenine molecules on single plasmonic gold quadrumer nanostructures with plasmonic Fano resonances [98]. Single-molecule sensitivity with the estimated $EF_{\text{SECARS/SPRS}}$ of $\sim 10^{11}$ was demonstrated on these molecules with small Raman cross sections. The linear scattering spectrum of the plasmonic substrate nanostructure was optimized to match the excitation and signal fields in order to suppress absorption of the pump field and to enhance scattering of the anti-Stokes signal by the subradiant and superradiant modes, respectively (Figure 10A and B). The quadrumer consisted of four coupled gold nanodisks whose diameters and gap sizes may be used as the control parameters to match the SPR and excitation/signal frequencies. The spatial overlaps between the field distributions need to be optimized so that the excitation hot spots from the pump, Stokes and probe lasers are in the same spatial

locations. Figure 10C and D shows spatial field enhancement intensity distributions and SECARS enhancement maps, respectively, indicating good localization in the center of the quadrumer and overlap. The evidence for signal molecule sensitivity was provided by the bi-analyte statistical analysis.

Next, we discuss the coherence effects in these single-molecule SECARS experiments. According to our previous theoretical analysis, the coherence enhancement effect may be expressed as the ratio of the number of photons generated through the CARS, $\langle n_4^{\text{coh}} \rangle$, to the number of incoherent spontaneously scattered Raman photons, $\langle n_4^{\text{incoh}} \rangle$, as

$$\frac{\langle n_4^{\text{coh}} \rangle}{\langle n_4^{\text{incoh}} \rangle} \cong \lambda^2 \frac{N(N-1)}{NV} \frac{|\rho_{bc}|^2}{\rho_{cc}} R, \quad (1)$$

where λ is the wavelength, V is the sample volume, R is the sample radius, ρ_{cc} is the population of the ground state c , ρ_{bc} is the coherence between vibrational levels b and c and N is the number of molecules [7]. Eq. (1)

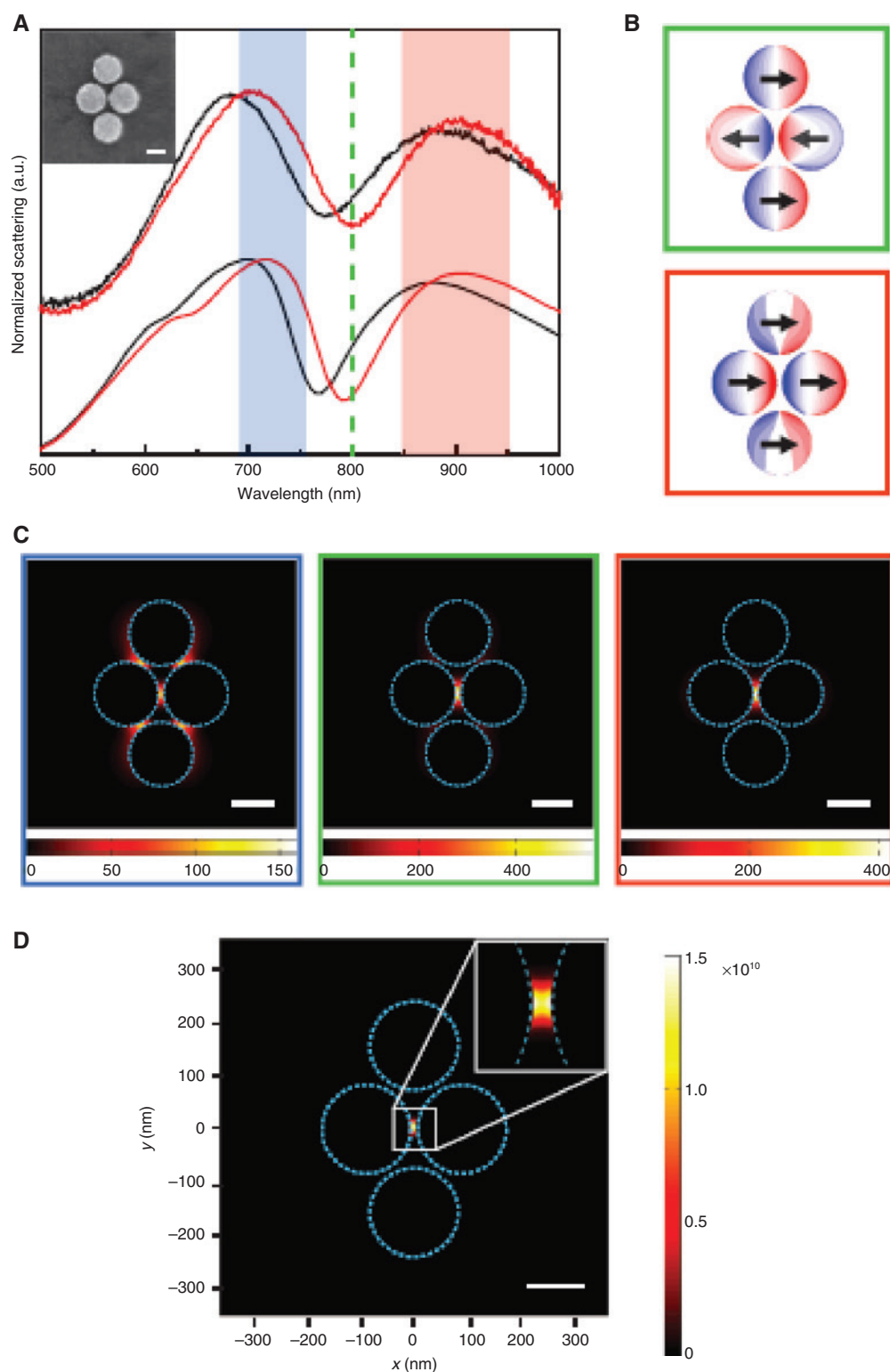


Figure 10: SECARS on a single gold quadramer nanostructure using a plasmonic Fano resonance.

(A) Experimental (top) and calculated (bottom) linear scattering spectra of a single quadramer without (black) and with (red) p-MA molecules. Green dashed line indicates the pump beam at 800 nm; red and blue zones show the Stokes and anti-Stokes scattering regions. The inset shows a scanning electron microscopy image of the quadramer. (B) Charge densities on the top surface of the quadramer excited at 800-nm pump (top) and 900-nm Stokes (bottom), corresponding to the subradiant and superradiant modes, respectively. (C) Field enhancement intensity distributions at the anti-Stokes (left), pump (middle) and Stokes (right) frequencies, and (D) the corresponding SECARS enhancement map. Scale bar, 100 nm. Adapted from Zhang et al. [98].

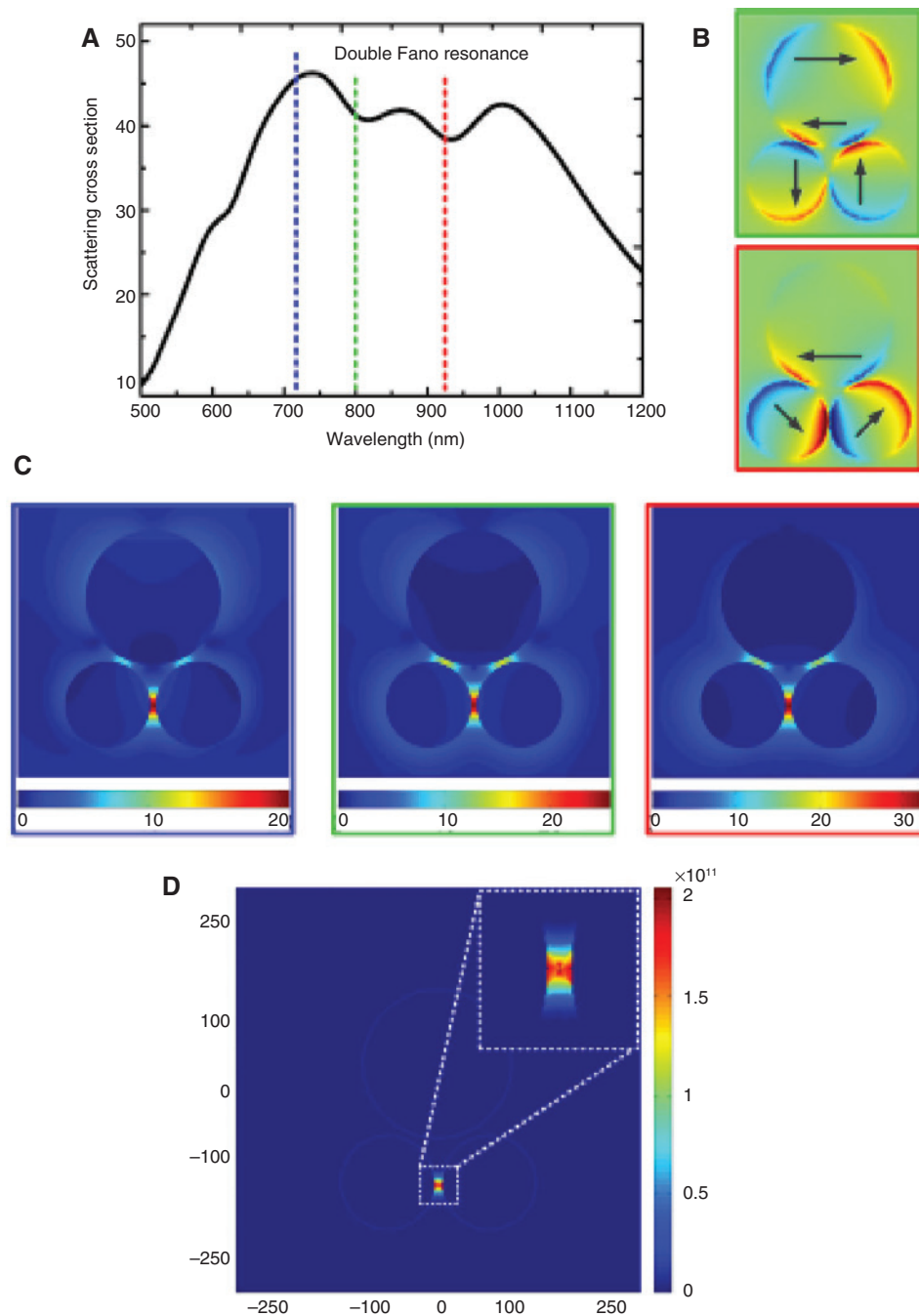


Figure 11: Optimal nanostructure design for SECARS.

(A) Scattering spectrum of the plasmonic gold disk trimer nanostructure. Blue, green and red dashed lines correspond to the anti-Stokes (710 nm), pump (800 nm) and Stokes (916 nm) fields. Two dips of the double Fano resonance are matched with the pump and Stokes fields to minimize absorption losses. (B) Spatial electric field distributions corresponding to the Fano resonance dips in (A) show two subradiant modes with out-of-phase oscillating electrons in the disks shown by arrows. (C) Near-field enhancement distributions in a plane 1 nm above the top surface of the trimer at the anti-Stokes (left), pump (middle) and Stokes (right) frequencies with the corresponding SECARS map in (D). Adapted from He et al. [93].

shows that in the single-molecule limit of $N=1$, the N^2 -type molecular coherence enhancement vanishes and the quantum coherence ρ_{bc} cannot be used to enhance the Raman signal. Intuitively, Eq. (1) shows that, for example,

at maximal coherence $\rho_{bc}=1/2$, the ratio of the coherent and incoherent signals is approximately proportional to the number of molecules N , that is, fields produced by the coherent emitters add up in amplitude such that the

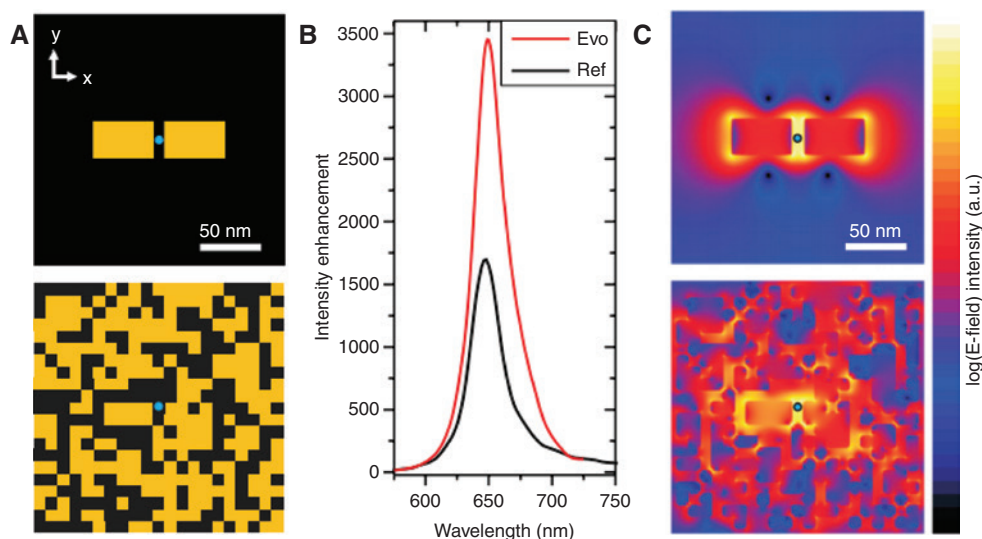


Figure 12: Optimal nanoantenna design.

Comparison between a resonant linear dipole nanoantenna with rectangular arms (A, top) and a matrix antenna nanostructure obtained with the evolutionary optimization (A, bottom). The scattering spectra in (B) are taken at the positions marked with blue dots in (A). (C) Near-field intensities at the two structures. Adapted from Feichtner et al. [129].

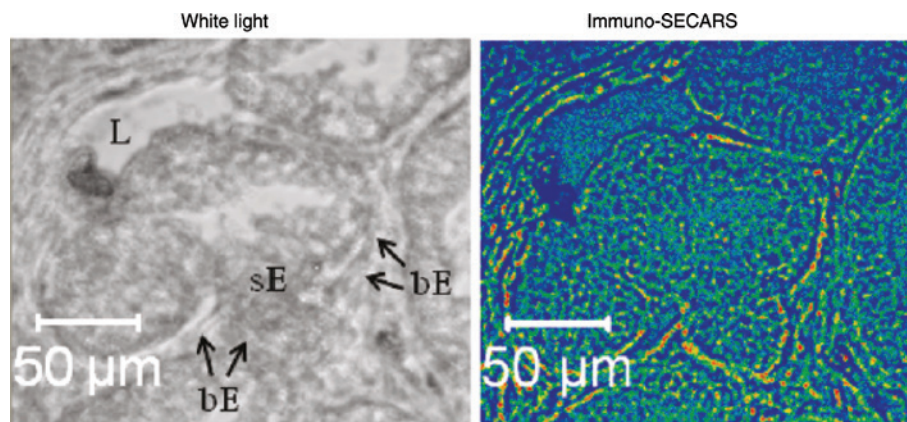


Figure 13: White light (left) and immune-SECARS (right) images of prostate tissue biopsies incubated with SERS-labeled p63 antibodies. The p63 protein is only abundant in the basal epithelium (bE, arrows) but not in the secretory epithelium (sE) or lumen (L) as shown by bright red spots in the immune-SECARS images. Adapted from Schlücker et al. [99].

intensity grows as the number of the coherent emitters squared, while the intensity of the incoherent emission is proportional to the number of emitters. In the limit of a single molecular vibrational oscillator, both signals will be equal and the coherence enhancement effect will be absent. In fact, the very term “molecular coherence” refers to a property of an ensemble and quantifies the relative “phasing” of ensemble members [121, 122]; the concept of coherence is unnecessary for the description of a truly single-oscillator process. Note that large molecules may consist of several, or many, (coupled) oscillators and, therefore, may exhibit the N^2 -type enhancement

mechanism, due to coherence among those multiple oscillators (within the single molecule). Coherence effects in multi-level quantum-mechanical systems, excited for example by pulsed laser fields, are of potential relevance to biological molecules. In a truly single-oscillator case however, the only remaining type of coherence, or phasing, is between the oscillator and an external reference, such as a pulsed laser field; this phasing may be used in the description of the heterodyne CARS or stimulated Raman techniques where this oscillator signal is coherently mixed with the external local oscillator field as described above.

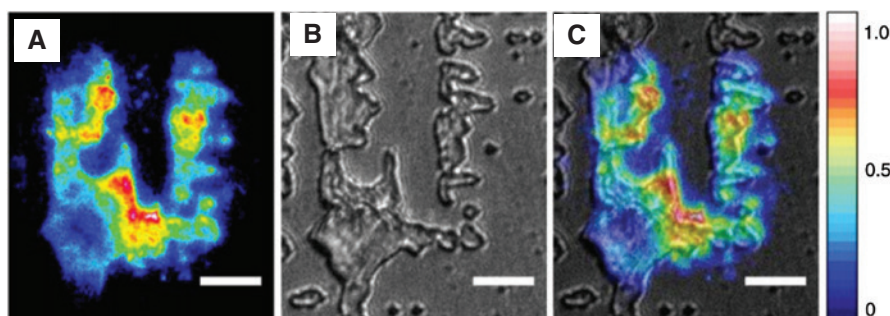


Figure 14: Wide-field SPP-based SECARS microscopy of lipid structures.

(A) SECARS, (B) transmission and (C) overlapped SECARS and transmission images of a thick aggregate of cholesteryl oleate. Scale bar, 20 μm . Adapted from Fast et al. [100].

4.6 Optimal nanostructure design

Next, we discuss strategies to optimize the nanostructured substrates to improve the SECARS efficiency. A previous discussion revealed the need for improving the near-field enhancement in the hot spots of the plasmonic nanostructures as well as the spatial overlap of the hot spot distributions of the pump, Stokes and probe fields. Fano resonances were used to improve the SECARS signals on plasmonic quadrumers [98]. These SECARS substrate designs may be further improved by varying the properties of the excitation laser fields and of the plasmonic substrates. For example, the properties of the plasmonic gold disk trimer were theoretically optimized to increase the SECARS signals by varying the incident laser excitation angle and using the double Fano resonance (Figure 11) [93]. The spatial near-field distributions of the pump, Stokes and probe showed hot spots in the same location in the trimer (Figure 11C). The good spatial overlap of the excitation fields and the suppressed absorption of the pump and Stokes placed in the dips of the double Fano resonance lead to the large predicted $\text{EF}_{\text{SECARS/CARS}}$ of $\sim 10^{11}$, which may be further increased to $\sim 10^{13}$ by reducing the inter-particle gap size. This substrate geometry provides several control parameters to tune the properties of the plasmonic response.

Nanostructured substrates may be optimized in a more general way using a large parameter space and evolutionary algorithms. Metal NP array geometries were optimized using evolutionary algorithms to produce broadband plasmonic field enhancement [123], collocated resonances [124] and improved SERS signals [125] and for guiding light at the nanoscale [126–128]. Optical nanoantennas were also designed using a large parameter space evolutionary optimization [129]. Figure 12 shows optimization of the near-field intensity

enhancement in a checkerboard-type array of gold cubes using an evolutionary algorithm, leading to the discovery of a new-type split-ring-two-wire antenna geometry [129]. The optimized matrix antenna (Figure 12A, bottom) has stronger near-field enhancement than the previous optical nanoantenna designs that were developed using a deterministic approach such as the linear dipole (Figure 12B) [44], cross [119], bow tie [130, 131] and Yagi-Uda [132, 133] antennas. The evolutionary optimization resulted in nanoantenna structural features, which gave insight into new design strategies such as the coupling of the electric and magnetic resonances. These new strategies may be used to improve the design of the SECARS substrates. Deterministic and evolutionary optimizations are effective strategies to design nanostructures with the controllable spatiotemporal near-field distributions, which may be used for investigating ultrafast dynamics of single and few biomolecules.

4.7 Biological applications

Only a few biological applications of SECARS were shown so far in spite of more than 30 years since the first demonstration. Immuno-SECARS microscopy was demonstrated as the first application of the SECARS detection contrast for bio-imaging using immuno-based staining techniques [99]. Figure 13 shows white light (left) and immuno-SECARS (right) images of prostate tissue biopsies labeled with p63-antibody-conjugated plasmonic NPs. The immuno-SECARS image shows an improved optical contrast providing a better localization of the p63 signals, fast imaging speed and suppression of the tissue autofluorescence background. In this biological imaging application, the SECARS signals were obtained from the Raman reporter labeling molecules conjugated to the plasmonic

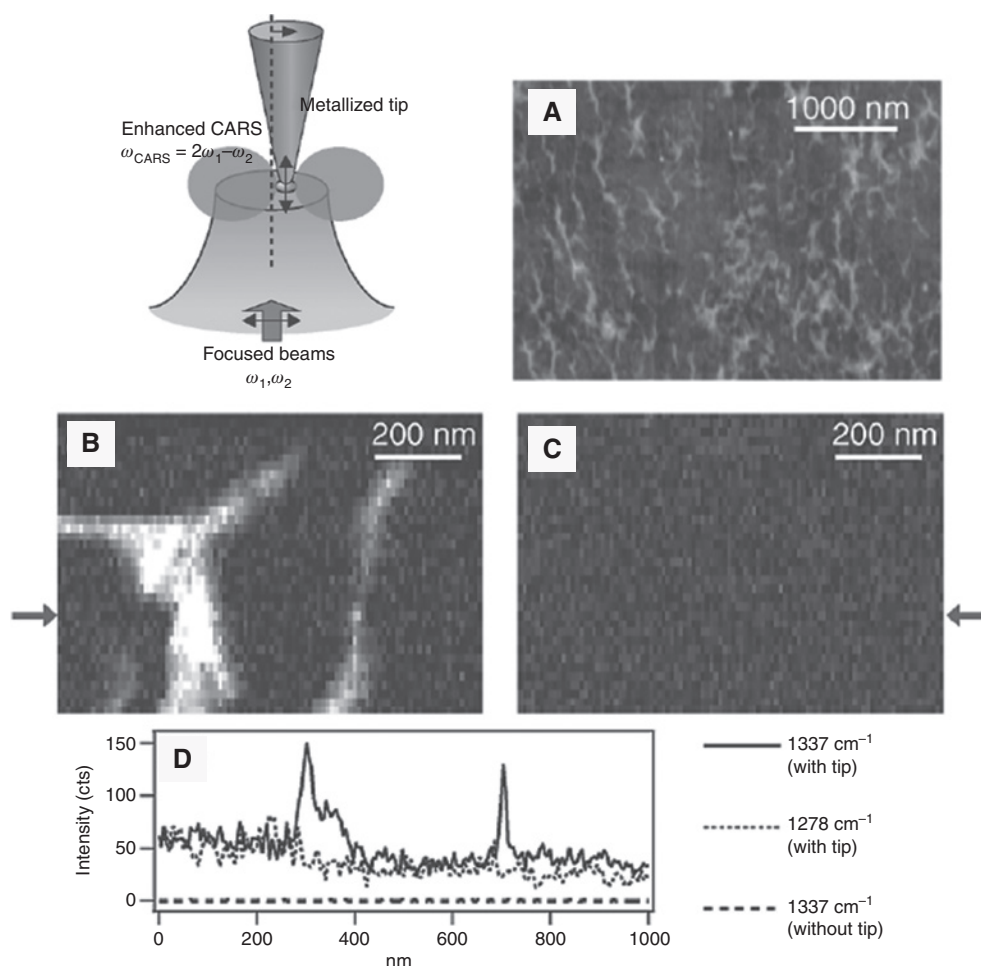


Figure 15: TECARS imaging of DNA network on a glass substrate using a metallized tip in a focused laser spot.

(A) Topographic image of the DNA network. (B) On-resonance and (C) off-resonance TECARS images and (D) the corresponding cross-sectional line profiles indicated by arrows. Adapted from Ichimura et al. [101].

NPs interacting with the prostate tissues via the antibodies attached to NPs. The immuno-SECARS microscopy takes advantage of the target-specific nanoprobe staining and may be performed with several types of staining agents simultaneously in the multiplex spectroscopic mode. This may allow for simultaneous imaging of different cell targets. Future developments may be used to optimize the efficiency of this technique to improve the speed and signal enhancement. Various labels may be used to target specific biological processes. Label-free SECARS may also be used for nanoscale bio-imaging using scanning probe microscopy as discussed below.

Label-free SECARS application to bio-imaging was shown in the wide-field SECARS microscopy of lipid structures on a 30-nm-thick flat gold substrate [100]. This implementation of SECARS microscopy followed the original demonstration of SECARS [81], using evanescent fields of SPPs to generate the coherent Raman

signals. Picosecond pump and Stokes laser beams were coupled to the gold surface via the Kretschmann configuration, and the reflected SECARS signal was detected in the epi-direction. High-contrast SECARS images of the aggregated cholesteryl oleate structures were obtained (Figure 14) using four orders of magnitude lower illumination density than in conventional CARS. This is advantageous for bio-imaging, where sample damage may easily occur due to overheating by intense ultrashort laser pulses. Future improvements of this technique may involve the suppression of the nonresonant FWM and two-photon photoluminescence backgrounds and weak CARS signals originating in the areas close to the lipid structures due to the back-coupling into the gold film (weak signals around the lipids in Figure 14). Promising future applications of SECARS to nanoscale imaging of cell membranes of whole cells in vivo may be achieved using this wide-field SECARS technique or by confining

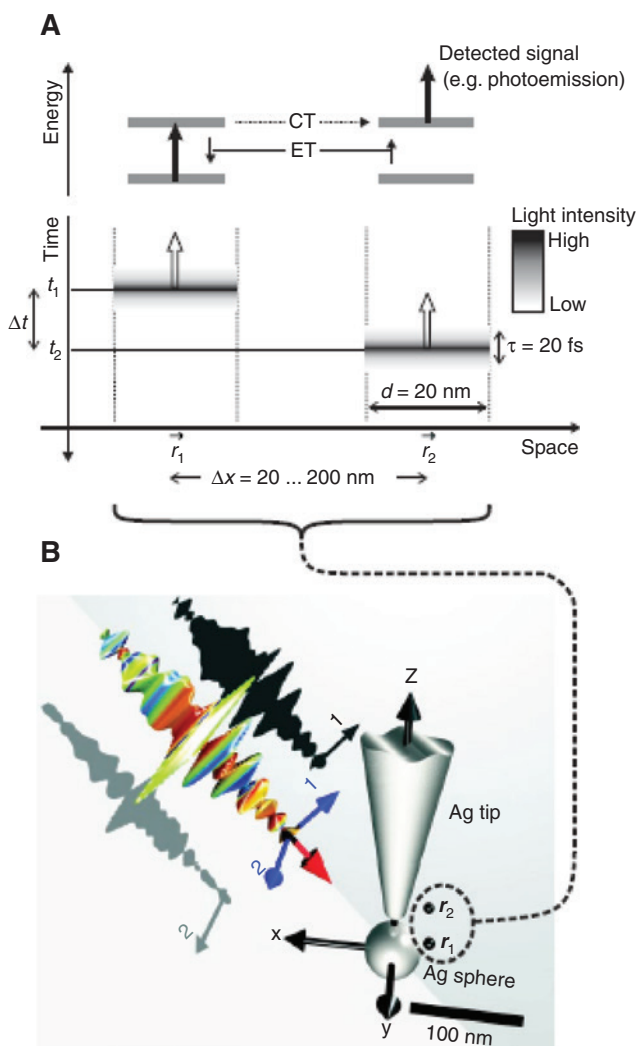


Figure 16: Near-field control.

(A) Schematic of ultrafast nanoscopic space-time-resolved spectroscopy. The objective is to study charge transfer (CT) or energy transfer (ET) ultrafast dynamics between two coupled quantum systems that are only a short distance apart with nanoscale spatial resolution and femtosecond temporal resolution. For example, the field first creates a local excitation at r_1 , and later the transferred excitation is detected at r_2 , for example, by photoelectron emission or SECARS. (B) The model nanostructure is illuminated by an optimized polarization-shaped femtosecond laser pulse which provides the designed spatiotemporal control of the electric fields to achieve the proposed objective. Adapted from Brixner et al. [134].

the excitation volume to the nanoscale using plasmonic scanning probes as described next.

4.8 TECARS

Similar to SERS bio-sensing, the TERS imaging of a small number of biomolecules with small Raman cross sections

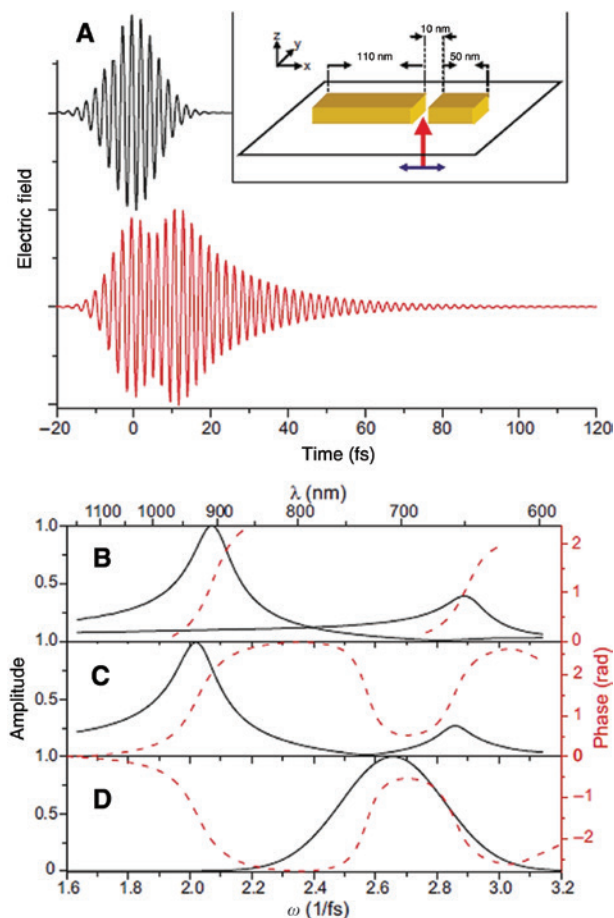


Figure 17: Control of optical nanoantenna response via phase compensation by laser pulse shaping.

(A) Time-dependent electric fields of the excitation source (black, top) and the corresponding near-field response (red, bottom) at the feed gap center of an asymmetric dipole antenna. (B) Impulsive spectral amplitudes (black solid lines) and phases (red dashed lines) of isolated 50- and 110-nm gold nanorods recorded at a point on the long axis of the rods, 5 nm from its end in air. (C) Impulsive spectrum (black solid line) and spectral phase (red dashed line) of the respective asymmetric antenna consisting of the two rods in (B), recorded at the center of the 10-nm gap. (D) Spectrum (black solid line) and phase (red dashed line) of a new source pulse with phase shaped as the opposite of the asymmetric antenna spectral phase shown in (C). Adapted from Huang et al. [135].

is challenging. In addition, the near-field enhancement of the tip is usually smaller than that of the nanostructured SERS substrates. Therefore, the combination of the surface enhancement of TERS and the coherence enhancement of CARS is promising for biological applications and has been demonstrated in several TECARS experiments [80, 88, 101–104].

The first TECARS imaging was shown on aggregated poly(dA-dT) DNA clusters with $\sim 20\text{-nm}$ height and $\sim 100\text{-nm}$ width and on DNA networks with $\sim 2.5\text{-nm}$

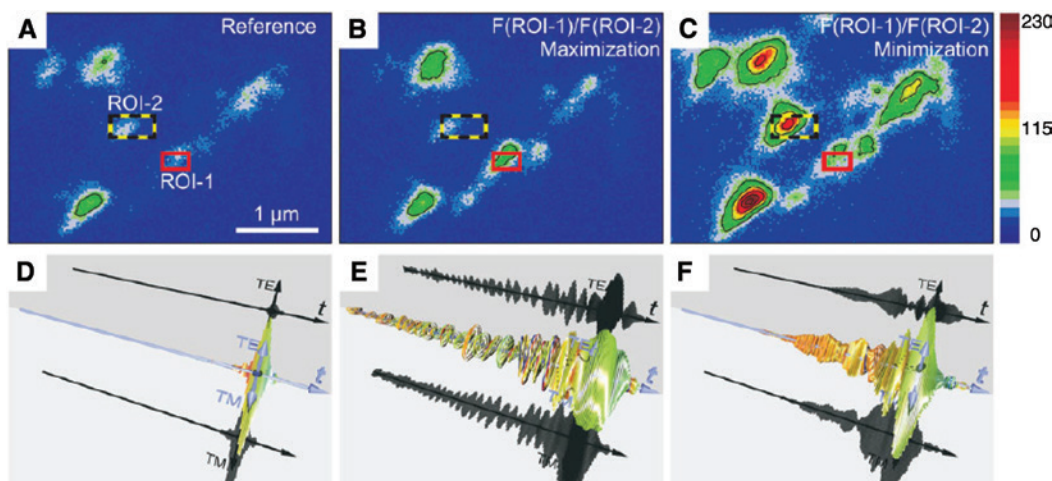


Figure 18: Near-field control of random plasmonic nanostructures by polarization laser pulse shaping. Contour plots of the photoelectron distributions on a plasmonic corrugated silver surface measured with PEEM are shown as obtained with unshaped transform-limited reference pulse (A and D) and adaptively optimized pulses maximizing (B and E) and minimizing (C and F) the ratio of the regions of interest ROI-1/ROI-2 shown by the dashed rectangles. (D–F) Corresponding optimal polarization-shaped laser pulses are shown in a quasi-3D representation with the time axis ranging from -1800 to 300 fs. Optimal pulses in (E) and (F) extend over much longer times and still lead to a “superenhancement” of the multiphoton photoemission signals. Adapted from Aeschlimann et al. [136].

height and up to few tens of nanometers width on a glass substrate using a silver-coated AFM probe and narrowband (~ 5 ps) laser excitation (Figure 15) [101]. Resonant excitation of the vibrational ring-breathing mode of adenine at ~ 1337 cm^{-1} resulted in the high-contrast nanoscale bio-imaging (Figure 15B). However, the non-resonant excitation at ~ 1278 cm^{-1} resulted in a poor contrast without significant structural features (Figure 15C). This first demonstration was followed by other TECARS experiments on DNA clusters [102], CNTs [88, 103] and polystyrene beads and mitochondria [104]. These results showed improvements in spatial resolution and signal strength compared to the conventional CARS microscopy. Broadband TECARS demonstrated a wide range of multiplex spectral imaging and ultrafast time-resolved measurement capabilities [103]. Radially polarized TECARS showed a sixfold increase of the signal compared to the linearly polarized TECARS [104]. However, in all these experiments, there were significant contributions of the nonresonant FWM and photoluminescence backgrounds from the tip which decreased the EFs and the imaging contrast. Future instrumentation improvements are envisioned that would optimize the signal-to-noise ratio by using the laser pulse shaping of the FAST CARS and by optimizing the tip geometry. The tip enhancement effect may be used not only for spectroscopic imaging but also for the manipulation of the near-field propagation dynamics in nano-plasmonic devices, which may also

be combined with near-field pulse shaping as discussed next.

4.9 Near-field control of nano-optical excitations

Near-field control by laser pulse shaping may be used to improve the performance of the nanoscale bio-imaging and to implement surface-enhanced FAST CARS. For example, the TECARS experiments described above may be improved by suppressing the nonresonant background using near-field pulse shaping in the analogy to the far-field FAST CARS. Also, the TECARS experiments may be designed to probe the ultrafast dynamics of nanoscale systems via the ultrafast nanoscopic space-time-resolved spectroscopy (Figure 16) [134]. Figure 16A shows the schematic of this technique, where a quantum system may be excited at the initial time t_1 at the location $\mathbf{r}_1$ and may be later detected at time t_2 at location $\mathbf{r}_2$, with the ultrashort time and space intervals of a few femtoseconds and a few nanometers, respectively. This could be implemented by the control of the spatiotemporal near-field distribution in the vicinity of a plasmonic nanostructure, such as a silver TERS tip (Figure 16B). This scheme will allow obtaining molecular movies with unprecedented control in the ultra-short space-time limit. Various processes may be investigated using optically and electronically detected signals

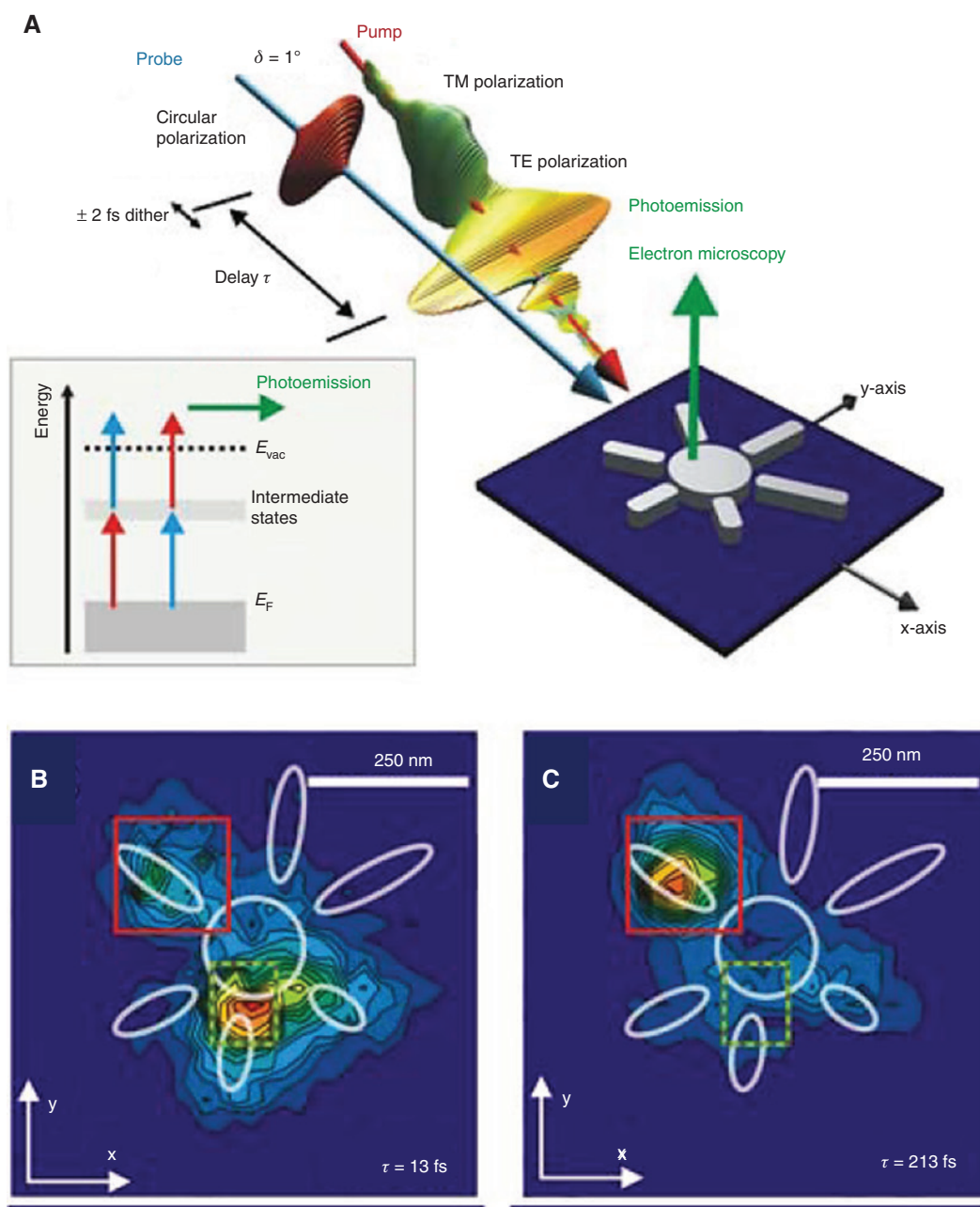


Figure 19: Spatiotemporal control of nano-optical excitations.

(A) Experimental scheme shows polarization-shaped pump and circularly polarized probe laser pulses illuminating the plasmonic sun-shaped nanostructure with an adjustable time delay τ . The inset shows two-photon excitation pathways for pump (red arrow) and probe interactions (blue arrow) that promote electrons from below the Fermi level E_F via intermediate states to above the vacuum energy E_{vac} . Normalized cross-correlation emission patterns for the two different delays $\tau = 13$ fs (B) and $\tau = 213$ fs (C) show two different hot spots located at different positions and different times with ultrafast nanoscopic control. Adapted from Aeschlimann et al. [138].

such as photoemission electron microscopy (PEEM) and SECARS.

Laser pulse shaping may also be used to enhance the near-field excitation and signal collection efficiency in resonant optical nanoantennas [48, 135]. For example, the complex spectral phase profiles in coupled plasmonic

nanostructures such as asymmetric dipole nanoantennas lead to the stretching of the temporal near-field amplitude profiles and, therefore, to the lower nonlinear optical signals such as SECARS. Such complex phase profiles may be compensated by laser pulse shaping, leading to temporal pulse compression (Figure 17) [135].

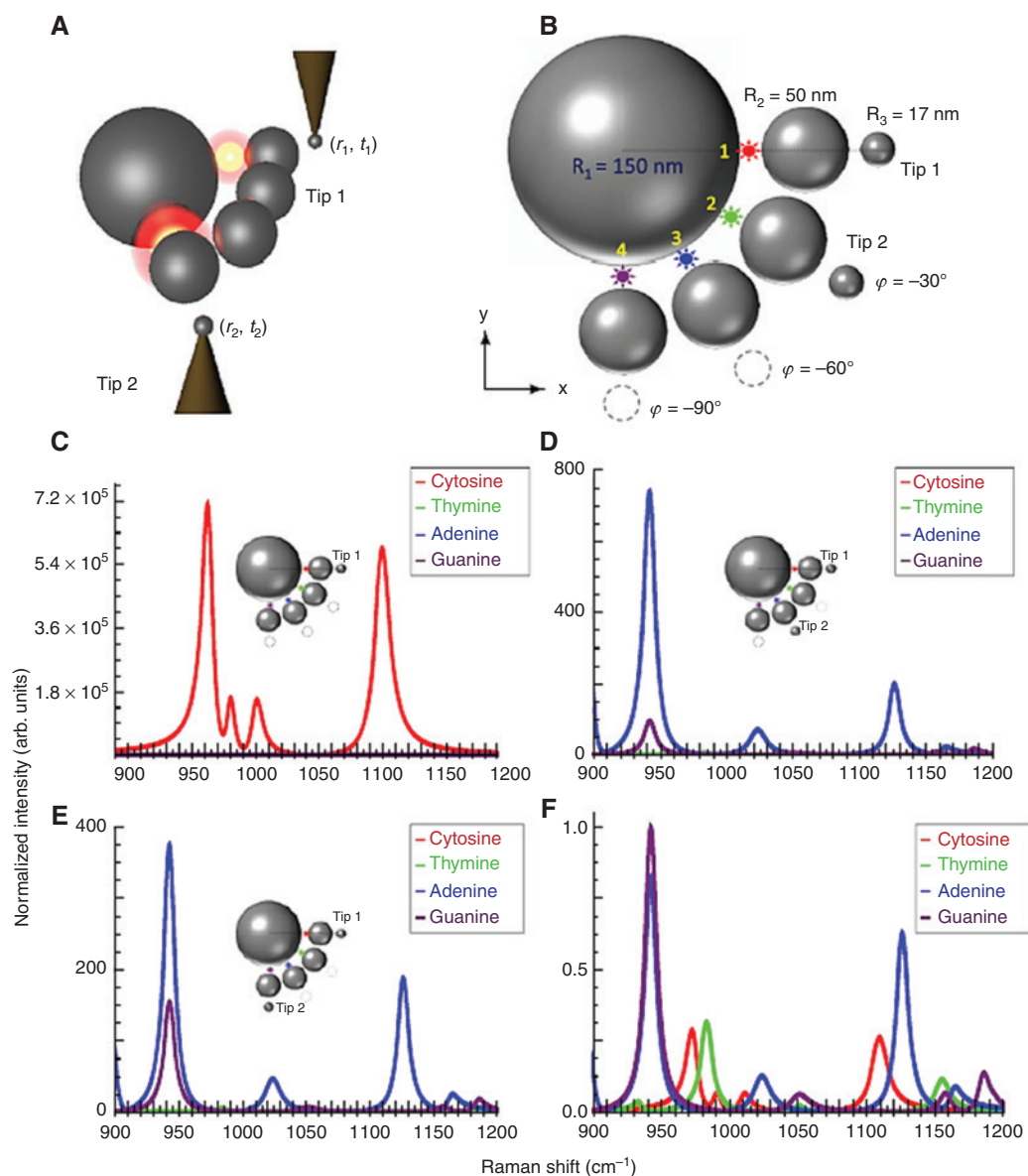


Figure 20: 2TECARS ultrafast nanoscopy using a plasmonic nanostructure made of self-similar nanolens antennas connected by a waveguide.

(A) Side view and (B) top view of the nanostructure and tips. The small nanospheres are attached to scanning probe microscope cantilevers, providing controlled subwavelength excitation and detection. Cytosine, thymine, adenine and guanine molecules are placed in the near-field hot spots of the nanostructure in the gaps between the large- and medium-size spheres, labeled 1–4 and highlighted by red, green, blue and purple stars, respectively. The position of tip 1 is fixed. The position of tip 2 is varied between the values of the angle φ : no tip 2, -30° , -60° and -90° . The nanostructure is excited by x-polarized ultrashort laser pulses. The dynamics of near fields and 2TECARS signals are controlled by changing the position of tip 2 and by laser pulse shaping. Simulated 2TECARS nanospectra with different positions of tip 2 provide isolated Raman signals from the selected molecules: x-polarized without tip 2 (C) and y-polarized with tip 2 at -60° (D) and -90° (E). (C) and (D) primarily generate signals from cytosine and adenine molecules, respectively. (F) CARS spectra of the mixture of four DNA nucleobases without the nanostructure do not show any significant selectivity and reveal strong signals from all molecules. Tip 2 is used as a nanoscale control “knob” for the selective detection of molecules via 2TECARS. Adapted from Ballmann et al. [139].

Complex pulse shapes may be used to optimize the near-field response in complex nanostructures with long-lived coherences (Figure 18) [136]. For example, large enhancement of the multiphoton photoemission

signals from a corrugated silver surface was obtained with complex polarization-shaped laser pulses (Figure 18B and C), resulting in the near-field “superenhancement”. Complex local phase distributions may result in the

decrease of the SECARS hot spots and may be optimized using this approach. Adaptive and analytic optimizations may be used to design optimal field shapes for specific targets [137].

Full spatiotemporal near-field control may be used to excite and probe different spatial locations with nanometer spatial resolution at different times with femtosecond temporal resolution. Figure 19 shows an example of the plasmonic sun-shaped nanostructure excited with optimally shaped pump and circularly polarized probe laser pulses to generate spatiotemporal near-field distributions with such desired properties. This ultrafast nanoscopic space-time near-field control may be used to probe charge and energy transfer dynamics in a variety of systems. PEEM or SECARS may be used as the signal detection method for probing the results of the near-field excitations. For example, plasmonic tips may be coupled to a nanostructure for performing near-field control and may be combined with pulse shaping and SECARS, as will be discussed next.

4.10 Ultrafast nanoscopy with multiple-tip TECARS: toward real space and time molecular movies

Simultaneous optimization of the nanostructure geometry and laser pulse shaping may be used to achieve the ultimate goal of recording molecular movies in real space and time. For example, we theoretically demonstrated a possibility of obtaining Raman signals from individual DNA nucleobases placed near a plasmonic nanostructure with femtosecond temporal and nanometer spatial resolutions (Figure 20). We used a plasmonic nanostructure made of self-similar nanolens antennas connected by a waveguide and placed cytosine, thymine, adenine and guanine molecules in the near-field hot spots of the gaps between the 50- and 150-nm spheres, labeled 1–4 and highlighted by red, green, blue and purple stars in Figure 20B, respectively. The nanostructure design was inspired by the plasmonic circuitry [135, 140] and the self-similar nanolens [141]. The position of tip 1 was fixed, forming an optical nanoantenna with the medium and large spheres oriented along the x axis. It generated a hot spot at position 1 for linearly polarized excitation. The near field at position 1 propagated along the waveguide formed on the surface of the large sphere, exciting other molecules in positions 2–4 at later times which were probed by tip 2. This forms the basis of the dual-TECARS (2TECARS) ultrafast nanoscopy [139], which takes advantage of the surface and coherence enhancement of the Raman signals and uses laser

pulse shaping to suppress the background from the undesired molecular signals in the analogy to FAST CARS. As a result, the specific molecular signals may be obtained from different spatial locations at different times, revealing the ultrafast plasmon propagation dynamics and energy or charge transfer within the coupled plasmon-molecular systems. These techniques may be applied to directly probe quantum energy and charge transport in photosynthetic systems [142–144].

5 Outlook

The future of quantum nano-biophotonics has been shaping in the form of new exciting technological developments and applications. Here, we described one of the best-of-both-worlds combinations of the coherence and SERS techniques, which provides nanoscale chemically specific and topographic information with ultrafast temporal resolution. Surface-enhanced FAST CARS offers a promising strategy to experimentally realize the predicted large EFs. Many other exciting ideas are on the horizon. Future experimental and theoretical developments need to address the discrepancies between the predicted and the observed surface-enhanced nonlinear optical signal enhancements.

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